2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO SELENIUM IN THE UNITED STATES

Since the publication of the previous version of ATSDR's Toxicological Profile for Selenium in 1996, several events have occurred that focused attention on the mineral selenium, its role in maintaining optimal human health, and any risk it may present to those exposed to excessive amounts of this metallic chemical element.

Late in the decade of the 90's, selenium was found to have entered the environment from old mining operations some northwestern U.S. locations. This resulted in public concern about the potential effects on livestock grazing in near-by areas, and ultimately the effects on humans consuming food products from plants and animals raised in those areas. At the same time, the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences was in the process of reevaluating the dietary requirements for many of the essential nutrients, including selenium. The result of this latter effort was the establishment a new Dietary Reference Intake (DRI) of 55 ug/day for selenium for both male and female adults (NAS 2000). This new number represented a decrease from the previous Recommended Dietary Allowance of 70 ug/day for male; 55 ug/day was already the RDA for females (NRC 1989). The combination of the increased concern regarding selenium toxicity and the reduction in the dietary selenium recommendation suggested that a reevaluation of selenium from a toxicological perspective might also be in order.

While a health guidance value equivalent to 5 ug/kg/day for selenium had been independently derived by both ATSDR and the U.S. EPA, this value was based upon data from two 1989 studies. To ensure that chronic oral MRL, which is used by a number of agencies at the federal, state, and local levels, is based upon the state-of-the-science knowledge about selenium, an update of the Toxicological Profile for Selenium was undertaken. Althugh the additional studies examined during this update effort did not result in a change in the MRL, they provide

strong support for the existing chronic oral MRL for selenium, thereby increasing our confidence in our health guidance value.

Selenium is a naturally occurring mineral element in the earth's crust. It is distributed widely in nature and is found in most rocks and soils at concentrations between 0.1 and 2.0 ppm. However, selenium is seldom found in its elemental form in the environment, but is obtained primarily as a byproduct of copper refining. Selenium exists in several allotropic forms. The primary factor determining the fate of selenium in the environment is its oxidation state. Selenium is stable in four valence states (-2, 0, +4, and +6) and forms chemical compounds similar to those of sulfur. The heavy metal selenide compounds (-2) are insoluble in water, as is elemental selenium. The inorganic alkali selenites (+4) and selenates (+6) are soluble in water and are, therefore, more bioavailable.

Conditions such as pH, oxidation-reduction potential, and the presence of metal oxides affect the partitioning of the various compounds of selenium in the environment. In general, elemental selenium is stable in soils and is found at low levels in water because of its ability to coprecipitate with sediments. The soluble selenates are readily taken up by plants and converted to organic compounds such as selenomethionine, selenocysteine, dimethyl selenide, and dimethyl diselenide. Selenium is bioaccumulated by aquatic organisms. Very low levels of selenium are found in ambient air.

Most processed selenium is used in the electronics industry. Selenium's semiconductor and photoelectric properties make it useful in "electric eyes," photographic exposure meters, and rectifiers for home entertainment equipment, and it is used to coat the metal cylinders from which a photographic image is transferred in xerography. Selenium is also used in the glass industry to counter coloration that results from iron impurities and in the production of both red and black glasses. Other uses include: as a component of pigments used in plastics, paints, enamels, inks, and rubber; as a catalyst in the preparation of pharmaceuticals, including niacin and cortisone; as a nutritional feed additive for poultry and livestock; in pesticide formulations; as an accelerator and vulcanizing agent in rubber production; as an ingredient in antidandruff shampoos (selenium sulfide); and as a constituent of fungicides (selenium sulfide). Radioactive selenium is used in diagnostic medicine and aids in the visualization of difficult-to-study malignant tumors.

The general public is exposed to selenium by ingestion of both organic and inorganic forms of selenium, which occur naturally in the diet. Most forms of selenium can interconvert either within organisms or within the environment, depending on ambient conditions. Some persons living in areas with high soil concentrations of selenium (as in areas of the western United States) might have higher exposure because

of the natural selenium levels found locally, particularly if they consume primarily crops grown in that area.

Various estimates of the selenium intake for Americans have ranged from 0.071 to 0.152 mg selenium/day. The greatest portion of dietary selenium intake occurs from the ingestion of grains and cereals. Selenium is excreted in breast milk, and levels vary with maternal nutritional status.

2.2 SUMMARY OF HEALTH EFFECTS

Selenium is known to be an essential micronutrient for humans and other animals; both inadequate and excessive selenium intake can cause adverse health effects. However, most people in the United States are unlikely to suffer from selenium deficiency. The current recommended dietary allowance (RDA) for selenium established by the Food and Nutrition Board of the National Research Council is 55 µg/day for adults. Adverse health effects due to selenium are generally observed at doses at least 5 times greater than the RDA.

Selenium deficiency has been associated with two endemic diseases found in selenium-poor regions of China: a cardiovascular condition known as Keshan Disease and an osteoarthropathy called Kashin-Beck Disease. Keshan Disease is characterized by cardiac enlargement, abnormal ECG patterns, cardiogenic shock, and congestive heart failure, with multifocal necrosis of the myocardium. The disease is reported to occur primarily in children and women of child-bearing age and has been successfully treated by selenium supplementation; however, a low incidence of cases persisting after selenium supplementation suggests that there may be other contributing factors. Kashin-Beck Disease is characterized by atrophy, degeneration, and necrosis of cartilage tissue, and occurs primarily in children between the ages of 5 and 13 years; it also has been successfully treated with selenium supplements. Chronically ill people and older people have been shown to have lower organ concentrations of selenium than healthy individuals, but it is not clear if this is a cause or consequence of aging or illness.

The primary target organ in humans and laboratory animals in cases of acute, high-level inhalation exposure to selenium is the lung, with cardiovascular, hepatic, nervous, and renal involvement as well. Lesser effects are observed in other organs/organ systems. Workers exposed to high concentrations of elemental selenium dust reported stomach pain and headaches, while workers briefly exposed to high levels of selenium dioxide dust reported respiratory symptoms such as pulmonary edema, bronchial spasms, symptoms of asphyxiation and persistent bronchitis, elevated pulse rates, lowered blood pressure,

vomiting, nausea, and irritability. No studies were located regarding effects in humans or animals after intermediate-duration inhalation exposure to selenium or to selenium compounds. For chronic inhalation exposure, there are several occupational studies that describe respiratory effects such as irritation of the nose, respiratory tract, and lungs, bronchial spasms, and coughing following exposure to selenium dioxide or elemental selenium dust. Respiratory symptoms similar to those reported for humans have been seen in animals inhaling high doses of elemental selenium fumes or dust, and studies of animals with acute inhalation exposure to hydrogen selenide or elemental selenium fumes or dust have reported hepatocellular degeneration and atrophy of the liver.

Acute oral exposure to high concentrations of selenium produces nausea, vomiting, and diarrhea in both humans and animals. Acute exposure of humans to selenium has occasionally produced cardiovascular symptoms, such as tachycardia, but no electrocardiographic abnormalities were found in 20 individuals from a human population chronically exposed to selenium. In contrast, acute and intermediate oral exposure of laboratory animals to selenium has produced myocardial degeneration.

Chronic oral exposure to high concentrations of selenium compounds produces selenosis, the major effects of which are dermal and neurological. As evidenced by populations in China, chronic exposure to high selenium levels in the diet can cause diseased nails and skin and hair loss. Higher levels can cause neurological problems including unsteady gait and paralysis. In contrast, however, studies of contemporary human populations living in areas of naturally occurring high selenium concentrations in the United States have not revealed adverse health effects in those populations. This difference may result from the lower exposure observed in the U.S. population compared to the Chinese population, as well as a better balanced, higher protein diet in the United States, which may increase tolerance to selenium.

Intermediate and chronic oral exposure of livestock to high levels of dietary selenium compounds also produces dermal and neurological effects. Studies in animals with high selenium concentrations demonstrate that many organ systems retain selenium and are affected. The primary effects in laboratory animals exposed to inorganic selenium salts or to selenium-containing amino acids are cardiovascular, gastrointestinal, hematological, hepatic, dermal, immunological, neurological, and reproductive. Blind staggers has been repeatedly observed in cattle feeding off vegetation in areas with high selenium content in the soil. However, the neurological effects have not been replicated in experimentally-exposed cattle receiving doses of selenium sufficient to induce hoof lesions, and thus, the neurological symptoms associated with blind staggers may be due to other compounds found within this vegetation.

Some evidence for adverse effects on the endocrine system has also been found following intermediate and chronic oral exposure to elevated levels of dietary selenium in humans and animals. Human studies have demonstrated a decrease in triiodothyronine levels in response to increased dietary selenium, although the hormone levels remained within the normal range. Intermediate-duration studies of rats have shown reductions in type-I-deiodinase activity in response to selenium. However, the levels of thyroid hormones in these animals did not show a consistent pattern.

There is no evidence to support a causal association between selenium compounds and cancer in humans. In fact, some epidemiological and experimental evidence suggests that selenium exposure under certain conditions may contribute to a reduction in cancer risk. Currently, the chemopreventive potential of selenium is under research. Selenium sulfide and ethyl selenac are the only selenium compounds that have been shown to be carcinogenic upon oral administration in rodents; however, significant exposure to these forms of selenium is extremely unlikely.

Studies of Chinese populations and laboratory animals exposed to high levels of organic and/or inorganic selenium compounds have not found evidence of selective teratogenic effects in mammals.

Selenosis. Following chronic oral exposure to excessive amounts of the organic selenium compounds found in food, the two principal clinical conditions observed in humans are dermal and neurological effects, as described most completely in the epidemiological study of endemic selenosis in the People's Republic of China. The dermal manifestations of selenosis include loss of hair, deformation and loss of nails, and discoloration and excessive decay of teeth, while neurological effects include numbness, paralysis, and occasional hemiplegia.

Similar clinical manifestations occur in livestock following intermediate and chronic exposure to excessive amounts (more than 30 times the normal dietary amount of selenium) of the organic selenium compounds found in seleniferous plants, including loss of hair and malformation of hooves in pigs, horses, and cattle and poliomyelomalacia in pigs. Histologically, swine with selenium-induced neurological signs exhibit bilateral macroscopic lesions of the ventral horn of the spinal cord. The selenium in the selenium-accumulating plant *Astragalus bisulcatus* appears to be a more potent neurotoxicant than D,L-selenomethionine or selenate. Following a similar dose of selenium, *A. bisulcatus* resulted in complete paralysis in four of five pigs after 5 days of treatment, and in the last pig after 3 weeks of treatment, while in pigs fed selenate, three of five developed complete paralysis, and one pig developed posterior paralysis after 4–21 days of treatment. Although D,L-selenomethionine resulted in

the greatest incidence of selenosis, it was the least potent neurotoxin, resulting in posterior paralysis in two of five pigs after 9 and 24 days of treatment. The pigs that did not develop paralysis were fed D,L-selenomethionine for approximately 31 days. The form of selenium in *A. bisulcatus* is unknown, although Panter et al. indicate that it is nonprotein.

The neurological signs and histopathology observed in livestock following oral exposure to excess selenium compounds have not been recorded in laboratory animals. This suggests that (1) small laboratory mammals may not be appropriate models for selenium toxicity in humans (e.g., laboratory animals absorb selenium compounds to a lesser extent, or metabolize and/or excrete selenium compounds more quickly), (2) some as yet unidentified organic form of selenium contributes to the neurological manifestations of chronic selenosis in humans and in livestock, or (3) unrecognized confounding factors, such as other plant toxins, have contributed to the neurological syndrome associated with chronic selenosis in field studies of humans and livestock.

Endocrine Effects. Selenium is a component of all three members of the deiodinase enzyme family, the enzymes responsible for deiodination of the thyroid hormones, and has a physiological role in the control of thyroid hormone levels. Significant decreases in triiodothyronine levels in response to elevated selenium have been observed in humans. However, the triiodothyronine levels observed in these studies were within the normal human range, so the biological impact of this change is unclear. The effect of increased dietary selenium on other thyroid hormones is also unclear. Intermediate-duration studies in rats show a decrease in type-I-deiodinase activity in response to elevated selenium; however, the levels of thyroid hormones in these animals did not show any consistent changes.

One of the most common effects observed following excess selenium intake in animals is a decrease in growth. It is likely that the selenium-induced reduction in growth has an endocrine component. For example, selenite treatment of young rats decreased somatomedin C levels, and growth hormone secretion in response to the growth hormone releasing factor was also reduced in selenium-treated rats. The primary endocrine target of selenium leading to decreased growth has yet to be elucidated.

Pancreatic toxicity has been observed following excess selenium exposure. Cytoplasmic flocculation was observed in lambs treated with a single oral dose of selenite, and pancreatic damage, which was not further described, was noted in rats following chronic oral treatment with selenate or selenite. Pancreatic toxicity associated with excessive selenium exposure is likely related to the unique ability of that organ to accumulate the element.

Hepatic Effects. Liver effects have not been reported for humans exposed to excessive amounts of selenium. No significant abnormalities were found in blood levels of liver enzymes of individuals living in high selenium areas, or in a "supersonic B" morphological examination of the livers of 20 individuals suffering from severe symptoms of selenosis. In experimental and other animals, however, the liver has been shown to be affected following both inhalation and oral exposure to several different selenium compounds. Hepatocellular degeneration was observed in guinea pigs following inhalation exposure to elemental selenium dust and hydrogen selenide. Cirrhosis, hepatocellular degeneration, and changes in liver enzyme levels in serum have been reported for rats, pigs, and mice orally exposed to selenite, selenate, or organic selenium. The doses in these studies producing adverse effects were approximately 10 times the amount normally found in an adequate diet. The liver appears to be the primary target organ for the oral toxicity of selenium in experimental animals following intermediate and chronic exposure, whereas liver cirrhosis or dysfunction has not been a notable component of the clinical manifestations of chronic selenosis in humans. Selenium sulfide administration has also produced frank hepatotoxicity in rats, but not in mice.

Renal Effects. No reports of renal effects in humans were located. In nonhuman animals, mild kidney effects have been observed following oral exposure to selenium compounds. These effects include hydropic degeneration in sheep exposed to selenite and nephropathy in monkeys exposed to selenomethionine. Rats appear to be more sensitive than mice to the renal effects of selenium compounds. A dose-related increase in renal papilla degeneration, described as mild to minimal, was observed in rats treated with selenate or selenite in the drinking water, while the only kidney effect noted in mice treated with sodium selenate or selenite in the drinking water was increased kidney weight. Selenium sulfide administration to mice has, however, been shown to produce interstitial nephritis.

Body Weight Effects. Two of the most common effects in experimental animals following intermediate or chronic oral administration of excessive inorganic and organic compounds of selenium are reduced growth rate of young animals and loss of weight in older animals. Selenium sulfide administration has been associated with reduced body weight in female mice. As noted under endocrine effects, it is quite possible that the decreased growth rate has an endocrine component.

Reproductive Effects. In samples from more than 200 men, no correlation between seminal fluid selenium and sperm count or mobility was detected. No significant increase in spontaneous abortions was reported among women chronically exposed to drinking water containing excessive amounts of selenium. Oral or injection treatment of rats with sodium selenate or selenite (at doses at least 8 times greater than those normally supplied by an adequate diet) has been shown to increase the number of abnormal sperm, produce testicular hypertrophy, or degeneration and atrophy in males, and to affect the estrous cycle in females. The animals in these studies were not mated, so it is not clear if fertility was affected. A small increase in the number of abnormal length estrous cycles was observed in mice exposed to selenium. Disturbances in the menstrual cycle (anovulation, short luteal and follicular phases) were also observed in monkeys treated orally with L-selenomethionine. Selenium deficiency has also been reported to cause decreased sperm production and motility in rats. The relevance of these reproductive effects of selenium in laboratory animals to potential reproductive effects in humans is not known.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

No MRLs were derived for inhalation exposure to selenium because of insufficient quantitative data concerning both human and animal exposures. Data on the health effects of inhaled selenium in humans are derived from studies of occupationally exposed workers. These studies suggest that the respiratory system is the most sensitive end point for inhaled selenium dust, but they do not provide quantitative measurements of exposure and are frequently confounded by concurrent exposure to other chemicals. Animal studies support the respiratory system as the target of selenium toxicity, but these are acute studies of exposure to high concentrations of selenium that also produced serious health effects and death.

Oral MRLs

No MRLs were derived for acute or intermediate oral exposure to selenium because of insufficient quantitative data concerning both human and experimental animal exposures. For acute exposure, no quantitative data are available from studies of humans. Some acute animal studies provide less serious LOAELs for organ weight changes, behavioral changes, and reduced body weight, which occur at doses similar to those producing serious LOAELs for paralysis and developmental effects in other studies. For intermediate exposure, one human study provided quantitative data suggesting that a selenium intake of 0.0048 mg/kg/day may affect thyroid hormone levels, but this study was available only as an abstract.

The effects seen in intermediate animal studies include reductions in enzyme activities, changes in liver and body weights, and histological changes in the liver and kidney. However, the relevance of animal models to selenium toxicity in humans is questionable. Humans with selenosis did not display any changes in serum levels of liver enzymes or morphological damage to the liver when examined by "supersonic B" examination, and the liver and kidney effects observed in animal studies occurred at doses ($0.2 mg/kg/day) that were considerably higher than those that produced changes in thyroid hormone levels in humans.

The chronic oral MRL is based on a study by Yang and Zhou. This study was an examination of a group of five individuals recovering from selenosis drawn from a larger population studied by the same authors. Yang et al. examined a population in an area of China where selenosis occurred. The study collected data on selenium levels in the diet, blood, nails, hair, urine, and milk of residents at three sites with low, medium, and high selenium, and compared the incidence of clinical symptoms of selenosis (morphological changes in finger nails) with dietary intake of selenium and selenium levels in blood. They found that selenium levels in blood corresponded to the dietary intake of selenium, and that symptoms of selenosis were found at or above a selenium intake level of 910 µg/day (0.016 mg/kg/day). In 1992, Yang and Zhou reexamined five individuals from the high selenium site who had been suffering from symptoms of selenosis (loss of fingernails and hair), but were recovering (nails were regrowing). Since their earlier report, the living conditions of the population had improved; they had been cautioned against consuming high selenium foods and parts of their locally produced corn had been replaced with rice or cereals. Yang and Zhou found that the concentration of selenium in the blood of these individuals had fallen from 1,346 µg/L (measured in 1986) to 968 µg/L (measured in 1992). Using a regression equation derived from the data in an earlier report, Yang and Zhou calculated that the dietary intake of selenium associated with selenosis in these individuals was 1,270 µg/day, while an intake of 819 µg selenium/day was associated with recovery.

- An MRL of 0.005 mg/kg/day has been derived for chronic oral exposure (>365 days) to selenium. This MRL is based on a NOAEL of 819 µg/day for disappearance of symptoms of selenosis in recovering individuals and uses an uncertainty factor of 3 for human variability. An uncertainty factor of 3 was considered appropriate, because the individuals in this report were sensitive individuals drawn from the larger population in the Yang et al. studies and because of the supporting studies. The MRL is consistent with the NOAELs observed for other human populations.